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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,847	01/09/2007	Kenneth Hofland	BJS-620-454	3278

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
12/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,847	HOFLAND ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 11/12/2009 has been entered.

The Request for Continued Examination filed 11/12/2009 has been carefully considered. The following information has been made of record in the RCE filed for the instant application:

1. Claim 5 has been canceled.

2. Claims 1 and 6-7 have been amended.

3. Remarks drawn to rejections under obviousness-type double patenting and 35 USC 103

The following rejections of record have been overcome:

The rejection of Claim 5 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim12 of U.S. Patent No. 6,265,385 ('385) and

The rejection of Claim 5 under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (WO 97/25044; cited in Search Report of 9/5/2006) in view of Palepu et al (US 4,963,551; cited in Search Report of 9/5/2006) have both been rendered moot by cancellation of claim 5.

Claims 1-4 and 6-10 are pending in the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (WO 97/25044 of record) in view of Palepu et al (US 4,963,551 of record).

Jensen et al teach a method of treating a CNS tumor in humans via administration of a topoisomerase-II poison and a bis-dioxypiperazine compound (page 38, lines 1-9). The bis-dioxypiperazine compound has structural formula (I) (page 11) and the specific compound used is denoted by the symbol ICRF-187 (same as recited in instant claim 3; page 14, lines 11-20). The topoisomerase poison is etoposide (page 40, lines 5-9). The patient can be treated

simultaneously or with different intervals between the two active agents (page 15, line 24 through page 16, line 24). According to Jensen, administration (to a human) of an effective amount of CNS tumor killing amount of a topoisomerase-II poison together with administration of a bis-dioxypiperazine compound, protects the non-CNS tissue of the patient (page 3, lines 18-26; page 7, lines 16-22). Any ratio of the topoisomerase II poison and the bis-dioxypiperazine combination wherein an increased effect is observed alone may be used (page 5, lines 11-14). When L1210 cells, which are known to metasize readily, were used, there was a trend towards a synergistic effect of the drug combination of etoposide and ICRF-187 (page 8, lines 18-25; page 10, lines 9-16). However, Jensen et al do not teach the use of radiation in their method of treatment.

Palepu et al teach the use of piperidinedione (abbreviated as ADR-529 and also known as ICRF-187) is a cardioprotective agent used in antitumor therapy and in addition to being a cardioprotective agent also acts as a sensitizer to ionizing radiation (col. 1, lines 27-36).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a topoisomerase II poison like etoposide and a dioxypiperazine like dexrazoxane in a method of treatment of CNS tumor in a subject and also use radiation treatment further as instantly claimed since the use of a combination of the topoisomerase poison and a dioxypiperazine for the same is taught in the prior art and the use of radiation in tumor/cancer treatment is also well known.

One of skill in the art would be motivated to make combined preparations and use the active agents in a method as instantly claimed since a dioxypiperazine like dexrazoxane is known to protect the patient from the toxic effects of the topoisomerase II poison (Jensen, page 3, lines

4-12). This makes possible the use of higher doses of the topoisomerase poison. In addition to this, the dioxypiperazine also acts as a sensitizer to radiation, as taught by Palepu et al. Hence the combined use of the active agents and radiation treatment would have the maximum beneficial effect with reduced side effects.

Response to Applicants Arguments

Applicants have traversed the rejection of claims 1-4 and 6-10 under 35 USC 103 of record arguing that:

1. In the instant application the cells exposed to radiation therapy have had no exposure to the bi-dioxypiperazine. Accordingly there could have been no sensitization of those cells to radiation therapy. The bis-dioxypiperazine is a hydrophilic compound and has a poor blood brain barrier penetration and therefor cannot sensitize brain cells to ionizing radiation.

2. In Fig. 2B in the instant specification it has been demonstrated that the combination of the bis-dioxypiperazine, dexrazoxane with radiation therapy produced substantially the same results as the use of radiation therapy alone. Hence, at the time of filing one of ordinary skill in the art would not have been led to believe that the bisdioxypiperazine in the combination of Jensen would have sensitized the brain to ionizing radiation. It is surprising that synergism in the activity of bis-dihydroxypiperazine and topoisomerase poison could be so strongly enhanced when used together with whole brain radiation therapy.

Applicants' arguments have been considered but are not found to be persuasive.

According to Jensen ICRF-187 has a low concentration in cerebrospinal fluid (page 9, line 24-28). So, the brain should have been exposed to some amount of ICRF-187 and this

should provide some sensitization to radiation. Applicants have also admitted in the background section in the Specification (page 1, line 30 through page 2, line 2) that etoposide (the topoisomerase II poison) in combination with radiotherapy also results in synergistic cell kill. According to Jensen, etoposide passes the blood brain barrier (page 9, lines 24-26) and its concentration is high in CNS metastasis. Therefore, the combination of etoposide and radiation therapy should result in a synergistic effect. In addition to this any additional sensitization provided of the brain cells by the bisdioxypiperazine (ICRF-187) even though low in concentration, should have an additive effect. Hence, one of ordinary skill in the art would expect the combination of the topoisomerase II poison, the bisdioxypiperazine and radiation to produce an enhanced effect. This is obvious from the teachings of the prior art and applicants admission in the background section of the specification.

Conclusion

Claims 1-4 and 6-10 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/

Examiner, Art Unit 1623

/Shaojia Anna Jiang/

Supervisory Patent Examiner, Art Unit 1623